

oligonucleotide is an α -anomeric oligonucleotide. An α -anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β -units, the strands run parallel to each other
5 (Gautier *et al.*, *Nucl. Acids. Res.* 15:6625, 1987). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue *et al.*, *Nucl. Acids Res.* 15:6131, 1987), or a chimeric RNA-DNA analog (Inoue *et al.*, *FEBS Lett.* 215:327, 1987).

Antisense oligonucleotides of the invention can be
10 synthesized by standard methods known in the art, for example, by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides can be synthesized by the method of Stein *et al.* (*Nucl. Acids*
15 *Res.* 16:3209, 1988), and methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin *et al.*, *Proc. Natl. Acad. Sci. USA* 85:7448, 1988).

For therapeutic application, antisense molecules of
20 the invention should be delivered to cells that express GLUTX *in vivo*. A number of methods have been developed for delivering antisense DNA or RNA to cells; for example, antisense molecules can be injected directly into the tissue site. Alternatively, modified antisense molecules, which
25 are designed to target cells that express GLUTX (*e.g.*, antisense molecules linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface) can be administered systemically.

However, it is often difficult to achieve
30 intracellular concentrations of antisense molecules that are sufficient to suppress translation of endogenous mRNAs. Therefore, a preferred approach uses a recombinant DNA construct in which the antisense oligonucleotide is placed

under the control of a strong *pol* III or *pol* II promoter. The use of such a construct to transfect target cells in the patient will result in the transcription of sufficient amounts of single stranded RNAs that will form complementary 5 base pairs with endogenous GLUTX transcripts and thereby prevent translation of GLUTX mRNA. For example, a vector can be introduced *in vivo* in such a way that it is taken up by a cell and thereafter directs the transcription of an antisense RNA. Such a vector can remain episomal or become 10 chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA.

Vectors encoding a GLUTX antisense sequence can be constructed by recombinant DNA technology methods that are standard practice in the art. Suitable vectors include 15 plasmid vectors, viral vectors, or other types of vectors known or newly discovered in the art. The criterion for use is only that the vector be capable of replicating and expressing the GLUTX antisense molecule in mammalian cells.

Expression of the sequence encoding the antisense RNA can 20 be directed by any promoter known in the art to act in mammalian, and preferably in human, cells. Such promoters can be inducible or constitutively active and include, but are not limited to: the SV40 early promoter region (Bernoist *et al.*, *Nature* 290:304, 1981); the promoter contained in the 25 3' long terminal repeat of Rous sarcoma virus (Yamamoto *et al.*, *Cell* 22:787-797, 1988); the herpes thymidine kinase promoter (Wagner *et al.*, *Proc. Natl. Acad. Sci. USA* 78:1441, 1981); or the regulatory sequences of the metallothionein gene (Brinster *et al.*, *Nature* 296:39, 1988).

VI. Ribozymes

Ribozyme molecules designed to catalytically cleave GLUTX mRNA transcripts also can be used to prevent

translation of GLUTX mRNA and expression of GLUTX
polypeptides (see, for example, PCT Publication WO 90/11364;
Saraver et al., *Science* 247:1222, 1990). While various
ribozymes that cleave mRNA at site-specific recognition
5 sequences can be used to destroy GLUTX mRNAs, the use of
hammerhead ribozymes is preferred. Hammerhead ribozymes
cleave mRNAs at locations dictated by flanking regions that
form complementary base pairs with the target mRNA. The
sole requirement is that the target mRNA have the following
10 sequence of two bases: 5'-UG-3'. The construction and
production of hammerhead ribozymes is well known in the art
(Haseloff et al., *Nature* 334:585, 1988). There are numerous
examples of potential hammerhead ribozyme cleavage sites
within the nucleotide sequence of human GLUTX cDNA.
15 Preferably, the ribozyme is engineered so that the cleavage
recognition site is located near the 5' end of the GLUTX
mRNA, i.e., to increase efficiency and minimize the
intracellular accumulation of non-functional mRNA
transcripts.
20 The ribozymes of the present invention also include
RNA endoribonucleases (hereinafter "Cech-type ribozymes"),
such as the one that occurs naturally in *Tetrahymena*
Thermophila (known as the IVS or L-19 IVS RNA), and which
has been extensively described by Cech and his collaborators
25 (Zaug et al., *Science* 224:574, 1984; Zaug et al., *Science*
231:470, 1986; Zug et al., *Nature* 324:429, 1986; PCT
Application No. WO 88/04300; and Been et al., *Cell* 47:207,
1986). The Cech-type ribozymes have an eight base-pair
sequence that hybridizes to a target RNA sequence,
30 whereafter cleavage of the target RNA takes place. The
invention encompasses those Cech-type ribozymes that target
eight base-pair active site sequences present in GLUTX.

As in the antisense approach, the ribozymes can be